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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

(57) Abstract

Described herein is a pharmaceutical composition containing Vitamin D and calcium, comprising a binding agent chosen from among the group consisting of: propylene glycol, a polyethylene glycol presenting a molecular weight comprised between 300 and 1500, liquid paraffin or silicone oil, useful for the treatment of nutritional deficiency of calcium and Vitamin D in the elderly.

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PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

Scope of the invention

The present invention refers to pharmaceutical compositions containing Vitamin D and a calcium salt, the process for their preparation, and their use in the treatment of pathological forms involving loss of bone tissue in the elderly, such as osteoporosis, as well as in the prevention of illnesses linked to calcium metabolism in the elderly, such as those leading to fractures of the proximal femur or other non-vertebral fractures.

State of the art

The use of Vitamin D and calcium salts, either separately or in association, for various illnesses, among which those concerning calcium metabolism in the elderly, is already well documented in the state of the art. For example, in FR 2724844, the existence of a therapeutic association is claimed between Vitamin D and calcium salts in combating osteoporosis.

However, the Vitamin D and calcium-based pharmaceutical formulations available today still present a number of problems which render them not altogether acceptable.

The problems that had to be faced for the pharmaceutical compositions that are the subject of the present invention were in particular:

a) the homogeneity of distribution of Vitamin D_3 in the final mixture;

b) the properties of flow of the powder of the calcium salt used; and, when present,

c) the rate of reconstitution of the suspension to be prepared as and when required.

In fact, for the preparation of these formulations, normally Vitamin D is used in the so-called "coated" form, since it presents greater stability than the pure crystalline form.

The "coated" form, however, presents the disadvantage of consisting of small granules that are highly dense and smooth, which renders their distribution inside the final mixture even more problematic, this distribution in itself already being complex on account of the small amount of the vitamin involved in comparison

with the other constituents of the pharmaceutical compositions that are the subject of the present patent.

In addition, the calcium salt used for this type of preparations normally undergoes a granulation process (either damp or dry) to overcome the problems due to the poor characteristics of flow that it presents in its most widely used form, i.e., in the form of fine powder, which makes it unsuitable for processing using ordinary high output rate machines. However, the granules (including those obtained with specific excipients for favouring disgregation) present a poor disgregation rate, which is instead highly desirable for the pharmaceutical preparation in bags, both in order to guarantee a good level of bio-availability and to obtain a suspension to be prepared as and when required, in which the salt may be finely divided in order to reduce the rate of sedimentation of the suspension and eliminate the "sand" effect which is noted when granular suspensions of this type are taken.

There is therefore an evident need to have available new pharmaceutical formulations containing a Vitamin D-calcium association which may enable a high dosage of calcium mixed in a homogenous way with very low doses of Vitamin D (for example 1-2 g of calcium for 500 - 1000 I.U. of Vitamin D), may present a good stability, may have a high level of bio-availability, may be suited to being processed using high-speed production machines, and may be pleasant to take for the patient.

Detailed description of the invention

The pharmaceutical composition according to the invention makes it possible to overcome the aforesaid problems owing to a "granulation" of the calcium salt, at the rate of 1 - 2 g of calcium for 500 - 1000 I.U. of vitamin D, in the presence of propylene glycol or a polyethylene glycol presenting a molecular weight comprised between 300 and 1500 (for formulations that involve subsequent disgregation in water) or (in the case of pharmaceutical formulations that do not envisage subsequent disgregation) with liquid paraffin or silicone oil.

Surprisingly, the addition of the calcium salt to the above said glycols makes it possible to obtain, a tripl advantageous effect::

a) The even and diffus d distribution of the glycol over the calcium granules, as well as over the other components of the formulation, plays a "binding" eff ct on

the small granules of coated Vitamin D_3. In this way, there is an anchoring of the particles of the vitamin to the system, thus enabling its even distribution ;

b) The atypical granulation of the calcium salt, taking place with this agent, modifies the properties of flow just enough to obtain a mixture having characteristics of smoothness such as to enable its processing with high output machines;

c) The aforesaid modification of the properties of flow of the calcium salt however is not an obstacle to its complete re-dispersion, where this is required, once the aqueous suspension has been reconstituted.

Moreover the moistening effect exerted by the propylene glycol on the calcium phosphate must be considered. This effect renders the operation of reconstitution of a dispersion faster than the one obtainable without its use.

According to the invention particularly preferred is propylene glycol. In this connection it is important to note that the well-known sour taste of propylene glycol or somewhat bitter one of low-molecular-weight polyethylene glycols may be easily covered by the common excipients and sweeteners, without affecting the pleasantness of the resultant pharmaceutical composition.

As binding agents for pharmaceutical forms that do not have to be dispersed in water, the substances that have proved extremely useful, and hence constitute a subject of the present invention, are liquid paraffin and silicone oil. These components in fact make it possible to obtain the same aggregating effect as the previous excipients and an equivalent distribution of the active principles.

Among the various forms of Vitamin D used for the formulations according to the invention, Vitamin D_3, Vitamin D_2 and their mixtures are preferred.

The calcium salt used for the present invention is, for example, chosen in the group consisting of: phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate, and chloride.

Particularly preferred is calcium phosphate and, more particularly, tribasic phosphate.

Normally the quantity of calcium phosphate is comprised between 30 - 80% by weight calculated on the total composition.

The pharmaceutical compositions that form the subject of the present patent moreover comprise the usual moistening agents (e.g., sucrose palmitate); fluidifying agents (such as, colloidal silica); suspending agents (such as cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose); organoleptic correctors (such as, flavouring substances, citric acid); sweeteners (such as mannitol, sorbitol, saccharin salts, aspartame, etc.); and colouring agents (such as E110).

It must be noted that the pharmaceutical compositions according to the present invention are not suitable for dermatology applications (for example in the form of creams).

According to a preferred formulation (bags) the pharmaceutical composition of the present application contains the propylene or the polyethylene glycol in a quantity comprised between 5 - 15% by weight calculated on the total weight of the formulation.

Non-limiting examples of the present invention are the following:

Example 1

Lot for 6000 bags

The sucrose palmitate, citric acid and sodium saccharin are sifted using a sieve with 0.5-mm mesh.

The propylene glycol is distributed over the calcium phosphate in a high speed granulator by setting the following process parameters:

2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, 25% of the mannite required, the citric acid, and the sodium saccharin are added to the mixture.

The above is mixed for 6 minutes with impeller at 80 r.p.m. and chopper at 1500 r.p.m. until a homogeneous composition is obtained.

Prepared separately, in a cube mixer at a rate of 25 r.p.m. for 15 minutes, is a premix consisting of sucrose palmitate, microcrystalline cellulose and carboxymethyl cellulose, lemon flavouring, E110, the remaining part of the mannite, and the Vitamin D_3.

The mixture thus obtained is transferr d into the granulator and mix d with the rest of the preparation, according to the following parameters:

1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate thus obtained is distributed in the bags, which thus contain a preparation having the following composition:

Tribasic calcium phosphate (corresponding to 1200 mg of Ca^{++})	3.100 g
Cholecalciferol (Vit. D_3) 100 000 IU/g (corresponding to 800 IU)	0.008 g
Propylene glycol	0.800 g
E110	0.002 g
Colloidal silica	0.120 g
Lemon flavouring	0.100 g
Microcrystalline cellulose - MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

In a similar way, but using polyethylene glycol instead of propylene glycol, bags may be prepared containing a preparation having the following composition:

Tribasic calcium phosphate (corresponding to 1200 mg of Ca^{++})	3.100 g
Cholecalciferol (Vit. D_3) 100 000 IU/g (corresponding to 800 IU)	0.008 g
Polyethylene glycol 400	0.800 g
E110	0.002 g
Colloidal silica	0.120 g
Lemon flavouring	0.100 g
Microcrystalline cellulose - MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

Example 2 (tablets)

Preparation for 20,000 tablets

The liquid paraffin is distributed over the calcium phosphate in a high speed granulator, setting the following process parameters:

2 minutes with impeller at 80 r.p.m. and chopper turned off, followed by 2 minutes with impeller at 160 r.p.m. and chopper at 1500 r.p.m.

The colloidal silica, the carboxymethyl cellulose, the sodium saccharin and the orange flavouring are sifted using a sieve with a 0.5-mm mesh.

Vitamin D_3 is added to the above-mentioned components and the product is mixed using a cube mixer at a rate of 25 r.p.m. for 5 minutes.

The sorbitol is then added, and everything is mixed in the cube mixer for 10 minutes at 25 r.p.m.

This premix is transferred into the granulator and is mixed with the rest of the preparation, by setting the following process parameters:

1 minute with impeller at 140 r.p.m. and chopper at 1500 r.p.m., followed by 30 seconds with impeller at 140 r.p.m. and chopper turned off.

The granulate is compressed to the required weight to obtain tablets having the following composition:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
(corresponding to 800 IU)	
Liquid paraffin	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g
Orange flavouring	0.100 g
Sorbitol q.s. to	4.400 g

In the same way, using silicone oil instead of liquid paraffin, it is possible to obtain tablets having the following composition:

Tribasic calcium phosphat	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g

(corresponding to 800 IU)	
Silicone oil	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g
Orange flavouring	0.100 g
Sorbitol q.s. to	4.400 g

The pharmaceutical compositions that form the subject of the present invention were made for the purpose of being used in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent proximal femur fractures and other non-vertebral fractures. These pharmaceutical compositions may be used also to prevent osteoporosis induced by chronic treatment with corticosteroids.

I.U. as used in the present application means International Units and corresponds to the amount having the activity of 0.0025 γ of Vitamin D3.

CLAIMS

1. Pharmaceutical composition containing as active principles Vitamin D associated to a calcium salt characterized in that it comprises a binding agent chosen in the group consisting of: propylene glycol, a polyethylene glycol presenting a molecular weight comprised between 300 and 1500, liquid paraffin or silicone oil and that the Vitamin D is present at the rate of 1 - 2 g of calcium for 500 1000 I.U. of Vitamin D.

2. Pharmaceutical composition according to Claim 1, in which the calcium used is in the form of a salt chosen in the group consisting of: phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate, and chloride.

3. Pharmaceutical composition according to Claims 1 and 2, in which the calcium salt is calcium phosphate.

4. Pharmaceutical composition according to Claim 3 wherein the calcium phosphate is 30 - 80% by weight calculated on the total composition.

5. Pharmaceutical composition according to Claim 1, in which the Vitamin D used is Vitamin D_2 (or ergocalciferol), Vitamin D_3 (or cholecalciferol), or one of their mixtures.

6. Pharmaceutical composition according to Claim 5, in which the vitamin used is Vitamin D_3.

7. Pharmaceutical composition (bag) according to Claim 1, containing the propylene glycol or polyethylene glycol in a quantity comprised between 5-15% by weight calculated on the total composition.

8. Pharmaceutical composition (tablet) according to Claim 1, containing liquid paraffin or silicone oil.

9. Pharmaceutical composition according to Claim 7, characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
(corresponding to 800 IU)	
Propylene glycol	0.800 g
E110	0.002 g

Colloidal silica	0.120 g
Lemon flavouring	0.100 g
Microcrystalline cellulose - MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

10. Pharmaceutical composition according to Claim 7, characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
(corresponding to 800 IU)	
Polyethylene glycol 400	0.800 g
E110	0.002 g
Colloidal silica	0.120 g
Lemon flavouring	0.100 g
Microcrystalline cellulose - MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

11. Pharmaceutical composition according to Claim 8, characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
(corresponding to 800 IU)	
Liquid paraffin	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g
Orange flavouring	0.100 g
Sorbitol q.s. to	4.400 g

12. Pharmaceutical composition according to Claim 8, characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100 000 IU/g	0.008 g
(corresponding to 800 IU)	
Silicone oil	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g
Orange flavouring	0.100 g
Sorbitol q.s. to	4.400 g

13. Process for the preparation of a pharmaceutical composition according to Claims 1 and 7, characterized by the following steps:

a) In a granulator turning at high speed, distribute the binding agent, consisting of propylene glycol or low-molecular-weight polyethylene glycols over the calcium salt.

b) Add the colloidal silica, approximately 25% of the mannite, the citric acid, and the sodium saccharin, and mix for the time required and at the appropriate speed.

c) Add the mixture, prepared separately, consisting of sucrose palmitate, a suspending agent, flavouring, colouring agent, the remaining part of the mannite, and the Vitamin D_3, and mix together with the rest of the preparation.

d) Distribute the granulate thus obtained into bags.

14. Process for the preparation of a pharmaceutical composition according to Claims 1 and 8, characterized by the following steps:

a) In a granulator turning at high speed, distribute the binding agent, consisting of liquid paraffin or silicone oil, over the calcium salt.

b) Add in order, to a mixture of colloidal silica, carboxymethyl cellulose and sodium saccharin previously sifted, the Vitamin D_3 and the sorbitol, mixing thoroughly every time before a new ingredient is added. Pour the mixture into the rotating granulator and mix for the required time and at the appropriate speed.

c) Compress the granulate to the required weight to obtain the desired tablets.

15. Composition according to Claim 1, for use in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone

tissue linked to age and to prevent femoral fractures and other non-vertebral fractures.

16. Composition according to Claim 1, for use in the prevention of osteoporosis induced by treatment with corticosteroids.

17. Method for the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures, in which therapeutically effective quantities of a composition according to Claim 1 are administered to the patient.

18. Method according to Claim 16 for the prevention of osteoporosis induced by treatment with corticosteroids.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 98/04567

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59 A61K33/06 A61K9/20 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 588 539 A (TEVA) 23 March 1994 see the whole document	1-7
X	FR 2 073 271 A (J. BOIVIN ET AL.) 1 October 1971 see the whole document	1,2,5,6, 8
A	WO 96 09036 A (LABORATOIRE INNOTHERA) 28 March 1996 cited in the application see the whole document	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/EP 98/04567

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 588539	A	23-03-1994	AT	148630	T	15-02-1997
			AU	667742	B	04-04-1996
			AU	4740893	A	24-03-1994
			CA	2106423	A	19-03-1994
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			JP	6219952	A	09-08-1994
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WO 9609036	A	28-03-1996	FR	2724844	A	29-03-1996
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			CA	2200568	A	28-03-1996
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			JP	10505850	T	09-06-1998
			NO	971356	A	21-03-1997
			PL	319585	A	18-08-1997

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
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ITALIE

Date of mailing (day/month/year)
23 November 1999 (23.11.99)

Applicant's or agent's file reference
1214PTWO

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/04567

International filing date (day/month/year)
21 July 1998 (21.07.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
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State of Nationality: LU
State of Residence: LU
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Facsimile No.:
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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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State of Residence: LU
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

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[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Philippe Bécamel

Telephone No.: (41-22) 338.83.38

ATENT COOPERATION TRE. .TY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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(Box PCT)
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Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 April 1999 (08.04.99)	
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International filing date (day/month/year) 21 July 1998 (21.07.98)	**Priority date** (day/month/year) 30 July 1997 (30.07.97)
Applicant VALLERI, Maurizio et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   24 February 1999 (24.02.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1214PTWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/04567	21/07/1998	30/07/1997
International Patent Classification (IPC) or national classification and IPC A61K31/59		
Applicant MENARINI INTERNATIONAL OPER. LUXEMB. S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/02/1999	29. 10. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer SANTOS, M Telephone No. +49 89 2399 8653

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/04567

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-7 as originally filed

Claims, No.:

1-18 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have b en considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16-17.

because:

☒ th said international application, or the said claims Nos. 16-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separat sh et

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	16-17 (see separate sheeet)

2. Citations and explanations

see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1: FR-A-2 073 271
   D2=EP-A-0 588 539
   D3=WO-A-9 609 036

2. The subject-matter of claims 1-17 is considered to be new and to involve an inventive step. Articles 33(2) and (3) PCT

   None of the documents cited in the search report discloses or suggests the pharmaceutical compositions according to claims 1-12 and 15-16, the process according to claims 13-14 or the method for the treatment according to claim 17.

   The closest prior art is considered to be documents D1 and D3.

   Document D1 relates to dermatological compositions useful for prevention of the aging of the skin (see page 3, lines 3-5). This document discloses a pharmaceutical composition comprising vitamin D associated to a calcium salt (any calcium salt which can be tolerated by the organism and assimilable by the skin) and paraffin oil. However, having regard to the teachings of D1, it is not possible to calculate, if the rate of vitamin D and calcium therein mentioned is

encompassed by present claim 1, since the only example in which the amounts are given does not indicate the IU/g of the vitamin D.

Document D3 relates to compositions for the treatment of osteoposoris comprising vitamin D and a calcium salt in the same rate as presently claimed. However, the binding agent of the compositions according to D3 is different from the binding agent according to the present compositions. The binding agent according to the present invention presents further advantages (see page 2, lines 29-32, page 3, lines 1-12 of the present application)

Document D2 does not contain calcium as active ingredient. Moreover, the proportion of ingredient d), i.e., the carrier or excipient, which may be lactose, sorbitol or calcium phosphate, is not given. None of the examples disclosed in D2 contain calcium phosphate.

The compositions according to the invention overcome the problems presented by the prior art compositions (see page 1, lines 16-32 and page 2, lines 15-20 of the present application). In particular, they enable high dosage of calcium with very low doses of vitamin D and present good stability. The pharmaceutical composition according to the present invention makes it possible to overcome the prior art problems owing to a "granulation" of the calcium salt at the claimed rate in presence of propylene glycol or a polyethylene glycol presenting a molecular weight comprised between 300 and 1500 (for formulations that involve subsequent disgregation in water) or (in the case of pharmaceutical formulations that do not envisage subsequent disgregation) with liquid paraffin or silicone oil. D1 does not suggests pharmaceutical compositions comprising the rate of vitamin D and calcium mentioned in present claim 1 and D2 does not suggest to use the claimed binding agents.
Thus, an inventive step can be acknowledged for the subject-matter of claims 1-17.

4. For the assessment of the present claims 16-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example,

does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREA.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1214PTWO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 04567	21/07/1998	30/07/1997
Applicant		
A. MENARINI INDUSTRIE FARMACEUTICHE R..... et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/04567

Box I Observations where certain claims were found unsearchable (Continuation of it m 1 of first sh t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 17
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/04567

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59 A61K33/06 A61K9/20 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 588 539 A (TEVA) 23 March 1994 see the whole document	1-7
X	FR 2 073 271 A (J. BOIVIN ET AL.) 1 October 1971 see the whole document	1,2,5,6, 8
A	WO 96 09036 A (LABORATOIRE INNOTHERA) 28 March 1996 cited in the application see the whole document	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/04567

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 588539 A	23-03-1994	AT 148630 T	15-02-1997
		AU 667742 B	04-04-1996
		AU 4740893 A	24-03-1994
		CA 2106423 A	19-03-1994
		DE 69307977 D	20-03-1997
		DE 69307977 T	28-08-1997
		DK 588539 T	10-03-1997
		ES 2098672 T	01-05-1997
		GR 3023127 T	30-07-1997
		JP 6219952 A	09-08-1994
		US 5565442 A	15-10-1996
		US 5804573 A	08-09-1998
		ZA 9306835 A	14-04-1994
FR 2073271 A	01-10-1971	NONE	
WO 9609036 A	28-03-1996	FR 2724844 A	29-03-1996
		AU 3168395 A	09-04-1996
		CA 2200568 A	28-03-1996
		DE 29521515 U	05-06-1997
		EP 0785769 A	30-07-1997
		FI 971188 A	20-05-1997
		HU 77702 A	28-07-1998
		JP 10505850 T	09-06-1998
		NO 971356 A	21-03-1997
		PL 319585 A	18-08-1997

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GERVASI, Gemma
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria 9
I-20122 Milano
ITALIE

NOTARBARTOLO & GERVASI
MILANO
RECEIVED
- 3 NOV. 1999

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29. 10. 99
Applicant's or agent's file reference 1214PTWO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/04567	21/07/1998	30/07/1997

Applicant
MENARINI INTERNATIONAL OPER. LUXEMB. S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing addr ss of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1214PTWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/04567	21/07/1998	30/07/1997
International Patent Classification (IPC) or national classification and IPC A61K31/59		
Applicant MENARINI INTERNATIONAL OPER. LUXEMB. S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/02/1999	29. 10. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer SANTOS, M Telephone No. +49 89 2399 8653

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/04567

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-7 as originally filed

Claims, No.:

1-18 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16-17.

because:

☒ the said international application, or the said claims Nos. 16-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sh t

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	16-17 (see separate sheeet)

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1: FR-A-2 073 271
   D2=EP-A-0 588 539
   D3=WO-A-9 609 036

2. The subject-matter of claims 1-17 is considered to be new and to involve an inventive step. Articles 33(2) and (3) PCT

   None of the documents cited in the search report discloses or suggests the pharmaceutical compositions according to claims 1-12 and 15-16, the process according to claims 13-14 or the method for the treatment according to claim 17.

   The closest prior art is considered to be documents D1 and D3.

   Document D1 relates to dermatological compositions useful for prevention of the aging of the skin (see page 3, lines 3-5). This document discloses a pharmaceutical composition comprising vitamin D associated to a calcium salt (any calcium salt which can be tolerated by the organism and assimilable by the skin) and paraffin oil. However, having regard to the teachings of D1, it is not possible to calculate, if the rate of vitamin D and calcium therein mentioned is

encompassed by present claim 1, since the only example in which the amounts are given does not indicate the IU/g of the vitamin D.

Document D3 relates to compositions for the treatment of osteoposoris comprising vitamin D and a calcium salt in the same rate as presently claimed. However, the binding agent of the compositions according to D3 is different from the binding agent according to the present compositions. The binding agent according to the present invention presents further advantages (see page 2, lines 29-32, page 3, lines 1-12 of the present application)

Document D2 does not contain calcium as active ingredient. Moreover, the proportion of ingredient d), i.e., the carrier or excipient, which may be lactose, sorbitol or calcium phosphate, is not given. None of the examples disclosed in D2 contain calcium phosphate.

The compositions according to the invention overcome the problems presented by the prior art compositions (see page 1, lines 16-32 and page 2, lines 15-20 of the present application). In particular, they enable high dosage of calcium with very low doses of vitamin D and present good stability. The pharmaceutical composition according to the present invention makes it possible to overcome the prior art problems owing to a "granulation" of the calcium salt at the claimed rate in presence of propylene glycol or a polyethylene glycol presenting a molecular weight comprised between 300 and 1500 (for formulations that involve subsequent disgregation in water) or (in the case of pharmaceutical formulations that do not envisage subsequent disgregation) with liquid paraffin or silicone oil. D1 does not suggests pharmaceutical compositions comprising the rate of vitamin D and calcium mentioned in present claim 1 and D2 does not suggest to use the claimed binding agents.
Thus, an inventive step can be acknowledged for the subject-matter of claims 1-17.

4. For the assessment of the present claims 16-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example,

does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

MILANO
RECEIVED
29 NOV. 1999

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 23 November 1999 (23.11.99)	
Applicant's or agent's file reference 1214PTWO	**IMPORTANT NOTIFICATION**
International application No. PCT/EP98/04567	**International filing date** (day/month/year) 21 July 1998 (21.07.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

MENARINI INTERNATIONAL OPERATIONS
LUXEMBOURG S.A.
Rue Dicks, 18
LU-Luxembourg
Luxembourg

State of Nationality	State of Residence
LU	LU

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

MENARINI INTERNATIONAL OPERATIONS
LUXEMBOURG S.A.
1, Avenue de la Gare
L-1611 Luxembourg
Luxembourg

State of Nationality	State of Residence
LU	LU

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Philippe Bécamel Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002968444

PATENT COOPERATION TREATY

NOTARBARTOLO & GERVASI MILANO
RECEIVED
13 MAG. 1999

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

Date of mailing (day/month/year)
22 April 1999 (22.04.99)

Applicant's or agent's file reference
1214PTWO

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/04567

International filing date (day/month/year)
21 July 1998 (21.07.98)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
A. MENARINI INDUSTRIE
FARMACEUTICHE RIUNITE S.R.L.
Via Sette Santi, 3
I-50131 Firenze
Italy

State of Nationality: IT
State of Residence: IT
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
MENARINI INTERNATIONAL OPERATIONS
LUXEMBOURG S.A.
Rue Dicks, 18
LU-Luxembourg
Luxembourg

State of Nationality: LU
State of Residence: LU
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Eugénia Santos

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002583879

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

NOTARBARTOLO & GERVASI
MILANO
RECEIVED
22 FEB. 1999

Date of mailing (day/month/year) 11 February 1999 (11.02.99)	
Applicant's or agent's file reference 1214PTWO	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP98/04567	21 July 1998 (21.07.98)	30 July 1997 (30.07.97)

Applicant
A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,HU,ID,IS,KE,
   KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,
   SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 February 1999 (11.02.99) under No. WO 99/06051

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

From the INTERNATIONAL BUREAU

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milan
ITALIE

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year)
08 April 1999 (08.04.99)

Applicant's or agent's file reference
1214PTWO

IMPORTANT INFORMATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP98/04567	21 July 1998 (21.07.98)	30 July 1997 (30.07.97)

Applicant
A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US,
   VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,HU,ID,IS,KE,KG,
   KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,UG,
   UZ,YU,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

Th International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Jean-Marie McAdams

Telephone No. (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP 98/04567

International Filing Date 21 JUL 1998 (21.07.98)

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 1214PTWO

Box No. I TITLE OF INVENTION

PHARMACEUTICAL COMPOSITIONS CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE

B x No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.r.l.
Via Sette Santi 3
50131 FIRENZE - ITALY

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: IT

State *(i.e. country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

B x No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

VALLERI Maurizio
Via Galliano 147
50144 FIRENZE - ITALY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: IT

State *(i.e. country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GERVASI Gemma
NOTARBARTOLO & GERVASI S.p.A.
Corso di Porta Vittoria 9
20122 MILAN - ITALY

Telephone No. 02/541799.1

Facsimile No. 02/54179920

Teleprinter No.

☐ Mark this check-box where no agent or comm n representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

TOSETTI Alessandro
Via F. Paoletti 13
50132 BAGNO A RIPOLI (Province of FIRENZE) - ITALY

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: IT

State *(i.e. country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* f nationality:

State *(i.e. country)* f residence:

This person is applicant f r the purposes f: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated n an ther c ntinuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania
- [X] AM Armenia
- [X] AT Austria
- [X] AU Australia
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina
- [X] BB Barbados
- [X] BG Bulgaria
- [X] BR Brazil
- [X] BY Belarus
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China
- [X] CU Cuba
- [X] CZ Czech Republic
- [X] DE Germany
- [X] DK Denmark
- [X] EE Estonia
- [X] ES Spain
- [X] FI Finland
- [X] GB United Kingdom
- [X] GE Georgia
- [X] GH Ghana
- [X] GM Gambia
- [X] ~~GW Guinea-Bissau~~
- [X] HU Hungary
- [X] ID Indonesia
- [X] IL Israel
- [X] IS Iceland
- [X] JP Japan
- [X] KE Kenya
- [X] KG Kyrgyzstan
- [X] KP Democratic People's Republic of Korea
- [X] KR Republic of Korea
- [X] KZ Kazakhstan
- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova
- [X] MG Madagascar
- [X] MK The former Yugoslav Republic of Macedonia
- [X] MN Mongolia
- [X] MW Malawi
- [X] MX Mexico
- [X] NO Norway
- [X] NZ New Zealand
- [X] PL Poland
- [X] PT Portugal
- [X] RO Romania
- [X] RU Russian Federation
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia
- [X] SK Slovakia
- [X] SL Sierra Leone
- [X] TJ Tajikistan
- [X] TM Turkmenistan
- [X] TR Turkey
- [X] TT Trinidad and Tobago
- [X] UA Ukraine
- [X] UG Uganda
- [X] US United States of America
- [X] UZ Uzbekistan
- [X] VN Viet Nam
- [X] YU Yugoslavia
- [X] ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [ ] .....
- [ ] .....
- [ ] .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) ITALY	(30-07-97) 30th July 1997	FI97A000184	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / _____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date *(day/month/year)*:	Number:
EPO	15th January 1998	RS 99775 IT

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	:	4	sheets
2. description	:	7	sheets
3. claims	:	4 (5)	sheets
4. abstract	:	1	sheets
5. drawings	:		sheets
Total	:	16 (17)	sheets

This international application is accompanied by the item(s) marked below:

1. [X] separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. [X] priority document(s) *identified in Box No. VI as item(s):*
5. ☐ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. [X] other *(specify)*: accompanying letter

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

GERVASI Gemma

Milan, July 16, 1998

For receiving Office use only

1. Date of actual receipt of the purported international application: (21.07.98) 21 JUL 1998
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau: